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T Cell Metabolism in Autoimmune Diseases

Dan Li, Miranda Piccioni, Zhimei Gao, Chen Chen, Zuoqia Chen, Jia Nie, Zhao Shan, Yangyang Li, Andy Tsun and Bin Li

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1. Introduction

Metabolism generates energy for organisms to sustain all kinds of biological functions, such as cell growth and cell apoptosis. The immune system requires an adequate energy supply for its optimal function [1]. During the activation and differentiation of T cells, the balance between glycolysis and lipid oxidation shifts in order to cater for the cell's energy requirements [2]. There is increasing evidence that shows how metabolism has an important role in regulating immunity, and a series of molecules have been described to play a functional role in both metabolism and the regulation of immune responses [3; 4; 5]. Uncovering the transcriptional regulation of the proteins participating in these metabolic processes allows us to understand how metabolism regulates T cell fate [6]. A set of non-coding RNAs called microRNA (miRNA), can also regulate these metabolic networks by binding to the 3'UTR of its target transcripts [7; 8; 9].

Autoimmune diseases were thought to be primarily caused by the immune response towards self-antigens. Organ-specific autoimmune diseases, such as multiple sclerosis, thyroiditis and type I diabetes, tend to arise due to T cell-mediated damage [10]. Abnormal metabolic changes may thus alter T cell function leading to the development of human diseases, including autoimmune diseases [11].

In this chapter, we highlight the recent research advances in metabolism, in particular to:

1. The role of metabolism in T cell differentiation and function.
2. The role of miRNAs in metabolic processes.
3. Dysregulation of metabolism during autoimmunity.

2. The role of metabolism in T cell differentiation and function

The role of cellular metabolism is to generate energy and supply biosynthetic demands in order to sustain normal biological functions. In the immune system, the control of cell

numbers and activity of different T cell subsets is important for generating an appropriate immune response to combat foreign pathogens and prevent the risk of developing autoimmunity. The fate of T cells is strongly linked to metabolism by regulating cell growth, survival, function and differentiation.

Naive T cells, having undergone positive and negative selection in the thymus [12; 13], enter the periphery and encounter their specific cognate antigens in the context of major histocompatibility complexes to become activated, and differentiate into effector T (Teff) or induced regulatory T (Treg) cells. Metabolically, naive T cells consume glucose and other essential nutrients at a low rate, enough to supply energy to maintain normal housekeeping functions [14]. Importantly, naive T cells require extrinsic signals to maintain sufficient levels of glucose metabolism to prevent atrophy and apoptosis [15].

T cells are activated through the T cell receptor (TCR) and CD28 by the engagement of MHC-peptide complexes and B7 family members on antigen presenting cells. During this process, the physiological and phenotypic repertoire of the T cells develop in a way to support rapid cell growth, proliferation, and the generation of effector T cells, in which metabolism plays a critical role [16]. To drive enhanced glucose metabolism in activated T cells, the upregulation of expression and trafficking of glucose transporter 1 (Glut1) is crucial [17] (Fig. 1). The downregulation of Glut1 in lymphoid cell lines can decrease proliferation and cause cell cycle arrest or apoptosis [18; 19]. In contrast, the transgenic overexpression of Glut1 in T cells increases cell size, cytokine production, and proliferation upon activation [20].

The expression of Glut1 in T cells is induced by activation with a strong TCR agonist or through the cross-linking of the TCR-associated CD3 protein [21]. Both the MAPK pathway (p38) and Myc activation are upstream of Glut1 activation [22; 23] and may mediate the TCR dependent control of Glut1. TCR signaling can also activate AMP-activated protein kinase (AMPK) [24], which upregulates glucose uptake to promote energy generation [25] and may be due in part to the upregulation of Glut1 expression. Following the loss of the TCR, naive T cells downregulate the expression of Glut1 [26]. Mitochondrial potential and cellular ATP levels are also reduced, which suggests the loss of glucose metabolism. Beside the TCR, interleukin (IL)-7 is also a key regulator of glucose uptake in T lymphocytes. IL-7 maintains glucose metabolism by promoting Glut1 trafficking [27]. The tyrosine residue at position 449 of IL-7R α is required for IL-7-mediated regulation of glucose uptake, which promotes rapid activation of signal transducer and activator of transcription 5 (STAT5) and a delayed yet sustained activation of Akt [28].

The intracellular trafficking of Glut1 is important for its localization to the cell surface to support glucose uptake. Co-stimulation through CD28 ligation can provide a strong signal to direct the trafficking of Glut1 to the cell surface through the activation of the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway [29]. Akt can be activated through the ligation of its N-terminal pleckstrin homology (PH) to phosphatidylinositol (3,4,5)-triphosphate (PIP3) at the plasma membrane, generated by PI3K from PIP2, and its subsequent phosphorylation by 3'-phosphoinositide-dependent protein kinase-1 (PDK-1) [30]. Once

activated, Akt can interact with and modulate the activity of different binding partners. The increased glucose uptake and augmented glycolysis observed upon CD28 co-stimulation can be prevented by LY294002-mediated PI3K inhibition [29], which induces a significant down-modulation of Glut1. Conversely, PI3K activation is inhibited by cytotoxic T lymphocyte antigen-4 (CTLA-4), results in Glut1 internalization where it is targeted to lysosomes for degradation and prevents the upregulation of glucose metabolism in activated T cells [31].

Although Glut1 plays a central role in T cell glucose metabolism, there are still other regulators downstream of the initial glucose uptake. For example, Akt increases hexokinase activity to increase glucose phosphorylation to prevent its transport out of the cell [32; 33]. In addition, Akt can also promote the activity of the key glycolytic enzyme, phosphofructokinase, by the phosphorylation of phosphofructokinase-2 and generation of the allosteric activator, 2,6-phospho-fructose [34]. Myc, better known as a regulator of proliferation and apoptosis [35], has also been shown to play a pivotal role in activation-induced glycolysis, being necessary for the upregulation of glycolytic enzymes and transporters. However, it still remains unclear as to how these pathways are integrated into T cell metabolism.

T cell activation induces a rapid elevation in oxygen consumption [36]; however, the most dramatic increase is in glycolysis. This results in the significant increase in the production of lactate, which can adequately guarantee an efficient but quick energy supply to the cell [1; 2; 37]. This glycolytic program supplies energy to T cells during their rapid differentiation, and the increase in intracellular glucose levels supports the pentose phosphate pathway required for the synthesis of nucleic acids, NADPH for producing ATP, and lipid synthesis [38]. This metabolism shift to high glycolysis can influence T cell function and survival. When glucose metabolism is limited in activated T cells, there is a decrease in the proliferation and production of interferon- γ (IFN- γ), and an increase in the expression and activation of pro-apoptotic Bcl-2 family proteins [39; 40].

Naive T cells can differentiate into different T cell subsets after stimulation, and during differentiation the metabolic program must match the demands of each cell function. Treg cells and T helper cells have different metabolic phenotypes: Treg cells prefer lipid oxidation and helper T (Th) cells prefer the glycolytic program. Different metabolic culture conditions can thus influence T cell differentiation *in vitro* [2]. The inhibition of mTOR and activation of AMPK can increase and decrease the percentage of Treg and Th cells, respectively [2]. Hypoxia-inducible factor 1 α (HIF1 α) is required for the upregulation of glycolytic activity, the promotion of Th17 differentiation and inhibition of Treg cell differentiation. HIF1 α is a key metabolic factor in the mTOR-dependent upregulation of glycolysis observed under Th17-skewing conditions [5] and negatively regulates Forkhead Box P3 (FOXP3) to inhibit Treg cell differentiation [41].

Leptin, a 16-kDa non-glycosylated protein encoded by the *ob* gene, is classically considered a hormone, as it regulates the balance between food intake and energy

expenditure. The level of serum leptin is levels is correlated directly with body-fat stores, increasing with fat accumulation and decreasing during fasting [4]. In recent years, leptin has been proved to be an immune response regulator. Mice with a genetic deficiency of leptin (*ob/ob*) or leptin receptor (*ObR*) have a reduced susceptibility to autoimmunity [42; 43]. Leptin has a specific effect on T cell responses partly by increasing Th1 and suppressing Th2 cytokine production. Also, leptin antibody can enhance the proliferation and suppress the function of Treg cells by down modulating the cyclin dependent kinase inhibitor p27 (p27kip1), and the phosphorylation of the extracellular-related kinases 1 (ERK1) and ERK2 [44].

There is still much unknown regarding the complete mechanisms of metabolism in T cell function in a physiological setting. These mechanisms could also be tissue specific, and the timing or strength of these signals could be crucial to the final fate of the T cell.

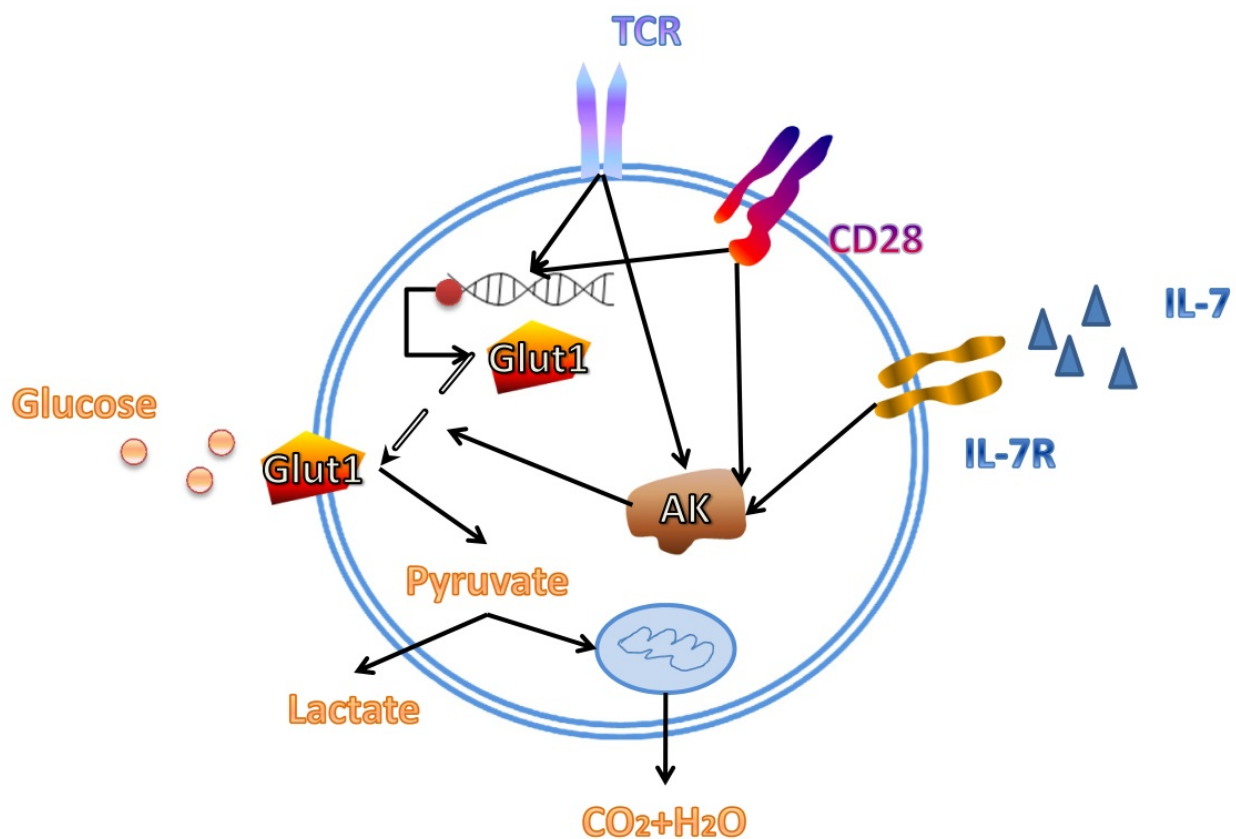


Figure 1. Glucose metabolism is activated by TCR, CD28 and cytokines in T cells. The increase in glycolysis is dramatic during T cell activation. In this process, the expression and intracellular trafficking of glucose transporter 1 (Glut1) is important as Glut1 controls the first step of glycolysis by facilitating the transport of glucose across the plasma membrane. The expression of Glut1 is upregulated by TCR and CD28 activation, while the trafficking to the cell surface is potentiated by signals from TCR, CD28 and IL-7 via Akt.

3. The role of miRNAs in metabolic processes

Metabolism interferes with the fate of T cells and plays a crucial role in the regulation of immunity. Cytokine/TCR signals and many growth factors have been reported to regulate metabolic processes [28; 29]. Moreover, microRNAs, a group of short non-coding RNA molecules that control gene expression by binding to the 3' untranslated region (UTR) of complementary target mRNAs, are also involved in the regulation of metabolic networks [45; 46]. Here, we summarize the recent findings of metabolism regulating miRNAs and whether they currently play a role in T cell perturbation either directly or indirectly.

Insulin-related cell signal pathways regulate glucose metabolism and are related to the development of diabetes. The first miRNA identified in this program is the evolutionarily conserved and islet-specific miRNA, miR-375, which regulates glucose-induced insulin secretion by inhibiting the expression of Myotrophin (Mtpn) [47]. Further studies have indicated that miR-375 is regulated by glucose and that miR-375 inhibits glucose-induced INS-1E cell proliferation via the targeting of PDK-1 [48]. miR-375 has also been found to affect palmitate-induced lipoapoptosis in NIT-1 cells, a NOD-derived β -cell line [49]; here, mir-375 increases the susceptibility to palmitate-induced lipoapoptosis by targeting Mtpn. Thus, miR-375 emerges as a novel pharmacological target for the treatment of diabetes. Additionally, it has been shown that miR-375 can regulate the expression of thymic stromal lymphopoietin, a Th2-skewing cytokine in epithelia to help control parasitic infection [50].

miR-9 is another miRNA that has a possible role in insulin secretion by targeting Onecut-2 (OC-2) [51]. As OC-2 is a negative regulator of granuphilin, which is known as a key regulator of insulin secretion by repressing insulin exocytosis [52], miR-9 is proposed to negatively regulate insulin exocytosis. Furthermore, miR-9 expression is regulated during glucose-stimulated insulin secretion and modulates Sirtuin 1 (Sirt1) expression *in vivo* [53], a deacetylase that has been implicated in stabilizing Treg cells by stabilizing the expression of its master transcription factor FOXP3 [54].

The Lin-28/let-7 axis is also involved in glucose metabolism. Overexpression of Lin28a/B in mice results in insulin sensitivity, enhanced glucose tolerance, and resistance to diabetes, while overexpression of let-7 has the opposite effect [7]. The insulin-PI3K-mTOR signalling pathway, which regulates growth and glucose metabolism can be activated by Lin28a/B and suppressed by let-7. let-7 target genes in human are associated with type 2 diabetes, and it is suggested that enhancing Lin28 or abrogating let-7 may be therapeutically promising for treating diseases such as obesity and diabetes. Although the role of this axis has not been extensively investigated in T cells, it has been shown that let-7 is involved in regulating the sensitivity of T cells to Fas-mediated apoptosis [55]. The mTOR signalling pathway has also been shown to be regulated by miR-199a-3p, which alters the susceptibility of tumour cells to hypoxia [56].

In cardiomyocytes, miR-133 reduces insulin-mediated glucose uptake by decreasing GLUT4 expression. miR-133 is believed to be expressed specifically in adult cardiac and skeletal

muscle tissues where it regulates the differentiation and proliferation of these cells [57]. It has been confirmed that the overexpression of miR-133 reduces the protein level of Kruppel-like factor 15 (KLF15) followed by its downstream target GLUT4. Silencing endogenous miR-133 *in vitro* increases the levels of KLF15 and GLUT4, which indicates a role of miR-133 in the metabolism of cardiac myocytes [8]. Insulin signalling can be regulated by miR-33a/b, which targets the insulin receptor substrate 2, an essential component of the insulin-signalling pathway in the liver [58]. miR-33a/b also regulates fatty acid metabolism by targeting several key enzymes involved in the regulation of fatty acid oxidation, including carnitine O-octaniltransferase, carnitine palmitoyltransferase 1A, hydroxyacyl-CoA dehydrogenase, Sirt6, and AMP kinase subunit- α [58]. Thus, miR-33a/b acts as a negative regulator of both insulin signalling and fatty acid oxidation in hepatic cell lines. There has yet to be any findings regarding the role of miR-133 and miR-33a/b in the modulation of T cells.

The liver specific miRNA, miR-122, is a key regulator of cholesterol and fatty-acid metabolism. Inhibition of miR-122 in the mouse liver results in reduced plasma cholesterol levels, increased hepatic fatty-acid oxidation, a decrease in hepatic fatty-acid and cholesterol synthesis rates, and the activation of AMPK [59]; interestingly, miR-122 can be induced by miR-370, which in turn induces lipogenic genes leading to the regulation of Cpt1 α [60]. Although primarily thought to be expressed in the liver, miR-122 has been shown to be expressed in lymphoma cells. Its upregulation protects these cells towards chemotherapy-induced cytotoxicity [61]. AMPK is also regulated by miR-451. In glioma cells it has been found that increased glucose levels upregulates miR-451 which in turn regulates the AMPK pathway to promote cell growth [62].

HIF1, shown to promote Th17 but inhibit Treg cell differentiation [41], has been found to upregulate miR-210 in hypoxic cells. This increase is proposed to provide tumour cells the ability to survive under stressful conditions [63; 64]. The negative regulation of HIF1 itself has been found through the miR-17-92 cluster [65], miR-22 [66], miR-20b [67; 68], and miR-519c [69], and positively regulated indirectly through miR-31 [70] by the downregulation of factor-inhibiting hypoxia inducible factor and miR-130 through the P-body protein DDX6 [71]. In turn, miR-31 and miR-210 negatively regulates FOXP3 expression in Treg cells [72; 73], which would correlate with their roles in positively regulating HIF1 responses and Th17, but not Treg differentiation. Interestingly, HIF1 α can also be negatively regulated by miR-155 [74], a miRNA that is highly upregulated in Treg cells induced by FOXP3 [75]. Also, miR-199a targets both HIF-1 α and Sirt1, and thus may play a role in Treg cell differentiation [76; 77]. The miR-17-92 cluster also promotes Th1 responses and prevents induced Treg cell differentiation [78]. Finally miR-130, has also been found to be upregulated upon TCR stimulation of CD8⁺ T cells, and downregulates CD69 during differentiation [79]. Even with the wealth of information above, there is a lack of evidence that these miRNAs regulate HIF1 in T cells to contribute to the control of the differentiation of various T cell subsets.

Recent studies have demonstrated that miRNAs are pivotal in T cell development and function [80; 81; 82], which indicates that miRNAs are one of the important regulators of the immune system. miRNAs have also been implicated in regulating metabolic pathways, mostly identified thus far in non-immune cells in controlling blood glucose levels (Fig. 2). More research is required to identify whether miRNAs are also involved in the metabolic regulation of T cells. The identification of miRNA signatures in various T cell subtypes may provide clues towards the cross-regulation between metabolism and miRNA networks in lymphocytes [83].

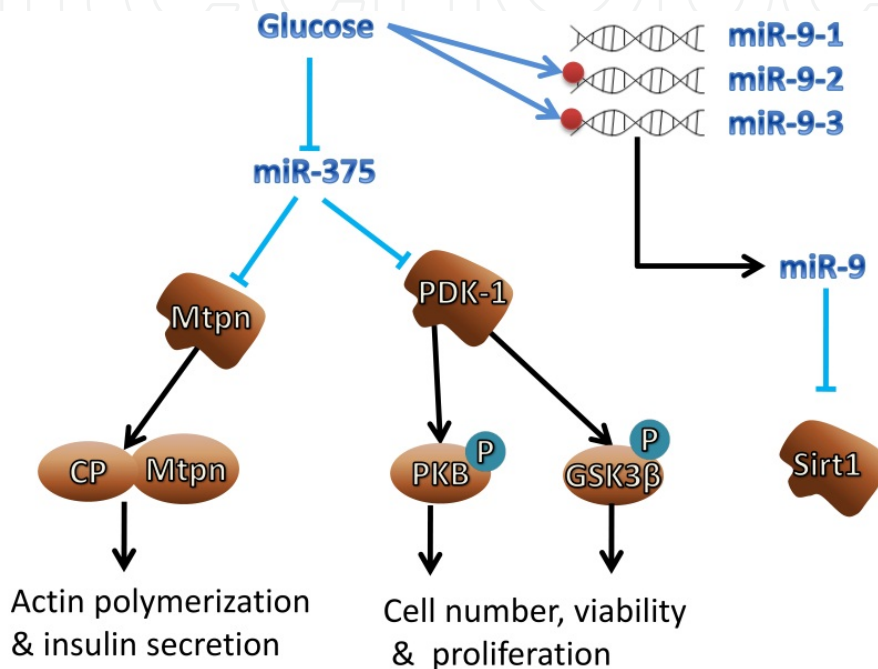


Figure 2. The regulatory network of microRNAs in pancreatic β -Cells. In pancreatic β -Cells some miRNAs participate in the insulin signal pathway. miR-375, which is downregulated by glucose, suppresses glucose-induced insulin secretion by inhibiting the expression of Myotrophin (Mtpn) and inhibits glucose-induced cell proliferation by targeting PDK-1. Glucose can enhance the expression of miR-9-2 and miR-9-3, which target Sirt1.

4. Dysregulation of metabolism during autoimmunity

The metabolic status of immune cells determines their fate and role in the immune system. The basic bioenergetic demands of resting lymphocytes can be essentially supplied by oxidative phosphorylation [84], while the increased amount of energy required during their activation implies a shift towards aerobic glycolysis. Much evidence exists regarding the role of Akt in the activation of mTOR, involved in a myriad of cellular processes, including translation, transcription, autophagy, growth and proliferation. mTOR is also known as a nutrient and energy “sensor”, since it regulates the expression of multiple nutrient transporters [85]. Several studies have indicated that the Akt and mTOR pathways are intimately connected, given that the latter can be modulated by Akt, which in turn seems to be sensitive to mTOR inhibition by rapamycin [86; 87].

Autoimmune diseases comprises a large number of pathologies characterized by exacerbated immune responses against self-antigens. The mechanisms leading to autoimmunity are not yet fully understood, but their multifactorial basis is almost clear. Given the involvement of these pathways in the activation and differentiation of multiple T cell subsets, it is conceivable that alterations in the expression and/or function of one or more of the factors involved can lead to a breakdown in immune homeostasis.

Indeed, both systemic and organ-specific autoimmune diseases seem to rely on genetic, infectious and environmental predisposing factors [88]. Systemic lupus erythematosus (SLE) is the prototype of systemic autoimmune diseases. Subjects affected are characterized by a strong hyperactivation of autoreactive CD4⁺ T cells and a consequent aberrant expansion of B lymphocytes. Large amounts of autoantibodies are secreted, mostly targeting nuclear antigens and affecting skin, joints, blood vessels and the central nervous system (CNS) [89]. Glomerulonephritis can also occur, due to deposition of immunocomplexes in the kidney. Several studies have found in SLE patients marked deficiencies in the number and/or suppressive capacity of CD4⁺CD25^{high} Treg cells [90; 91], although early works also identified the abnormal resistance to suppression of T_H17 cells as a major issue in the loss of tolerance characterizing SLE [92].

From a molecular point of view, current hypotheses support a sustained activation of the Akt-mTOR axis in SLE. In a well known model of murine lupus, the New Zealand Black White (NZBW)/F1 hybrid has an elevated expression and activation of Akt and mTOR at the glomerular level. Treatment of mice with rapamycin inhibits Akt and mTOR activation, thus prolonging mice survival and ameliorating the clinical course of the disease [93]. The hyperactivation of the Akt pathway in CD4⁺ T cells from MRL/*lpr* mice, a model of spontaneous lupus, could also be inhibited by the use of specific PI3K γ inhibitors [94]. An increase in Akt activation has been demonstrated in the peripheral blood from SLE patients, concurrently with an up-regulation of the phosphorylation of one of its downstream targets, GSK3 β [95], known as a negative regulator of cell cycle progression [96]. An abnormal activation of mTOR has been demonstrated in human SLE [97], and promising results in the treatment of the disease have been obtained with rapamycin, which could act by facilitating the differentiation of Treg cells and promoting the expansion of other subsets able to limit the T cell stimulation of auto-reactive B cells [98]. Beyond Akt and mTOR, a dysregulation in leptin expression has also been found in SLE patients [99; 100], but further studies are required to unlock the mechanisms that control its secretion.

A role for the Akt-mTOR axis has also been demonstrated in the pathogenesis of multiple sclerosis (MS). MS is an inflammatory disease of the central nervous system, characterized by the presence of CD4⁺ autoreactive T cells able to target myelin-based antigens, thus causing the progressive formation of demyelinating lesions and neuronal degeneration [101]. Given the target of inflammation, MS is considered an organ-specific autoimmune disease. Several studies have tried to clarify the role of different T cell subsets in MS, but the complex network of immune cells in this pathology does not make this an easy task. In particular, the role of the Treg subsets has not yet been clearly addressed. No

differences in numbers of Treg cells seem to exist between healthy subjects and MS patients, at least in the peripheral blood, and an increased number has been observed in the cerebrospinal fluid [102]. However, alterations in the Treg pool and function have been found [102; 103; 104]. Interestingly, gene-expression profile analysis of brains from post-mortem MS patients revealed a strong up-regulation of genes involved in cellular metabolism, such as Akt and HIF1 α [105]. This is consistent with the findings that T cells from HIF1 α ^{-/-} mice restimulated *ex vivo* with myelin oligodendrocyte glycoprotein (MOG) peptide display a reduced secretion of IL-17 and are poorly efficient to induce experimental autoimmune encephalomyelitis (EAE) in C57BL/6 mice [52]. Moreover, rapamycin administration is efficacious in treating EAE due to its dual action both on Treg and Teff cells [106]. The Akt-mTOR pathway seems to be subjected to leptin regulation during the development of EAE. Indeed, MOG-specific CD4⁺ T cells from leptin deficient (*ob/ob*) mice display a reduction in the activation of Akt and S6, downstream of mTOR. *Ob/ob* mice are resistant to adoptively transferred EAE [42; 107], a condition that can be restored by recombinant leptin administration [42]. In humans, increased levels of leptin has been detected in the CNS of MS patients [108].

Inhibitors of the mTOR pathway, such as sirolimus (rapamycin), are already used for the treatment of some autoimmune diseases, and many of its analogs constitute as promising candidates for a wide range of autoimmune diseases. Further study is required to reveal the metabolic signature of each disease in more depth, hence allowing the development of more specific and efficacious treatments.

A clear link has been established between Treg cells and type 1 diabetes (T1D), an inflammatory-autoimmune disease characterized by the inflammation and destruction of insulin-producing beta cells of the pancreas. This is particularly evident in individuals with IPEX (Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked syndrome), in which the lack of Treg cells is associated with an increased susceptibility to diabetes [109]. The onset and progression of the pathology does not seem to be related to an altered number of Treg cells, since most works have demonstrated that there are no differences between T1D subjects and healthy controls in the peripheral blood [110; 111]. Most likely, a decreased suppressive capacity of Treg cells and an enhanced resistance to suppression of Teff cells seem to be the basis of the loss of self-tolerance observed in T1D [112; 113]. What really is hidden behind the alterations in T cell functions is still a matter of debate, but results from an early study have pointed out a strong activation of Akt in splenocytes from NOD mice, which could be prevented by the use of the PI3K γ inhibitor AS605240 [114]. The amelioration observed in the clinical signs of diabetes after PI3K inhibition could be a consequence of the increase in Treg expansion as well as Teff suppression, probably due to the activation of cAMP response element-binding protein (CREB), a transcription factor shown to be involved in Foxp3 expression [115]. Anomalies in the number and function of T cell subsets have been also proved in other autoimmune diseases, such as rheumatoid arthritis (RA) [116] and psoriasis [117], but we are still far from clarifying the underlying molecular mechanisms behind their progression (Fig. 3).

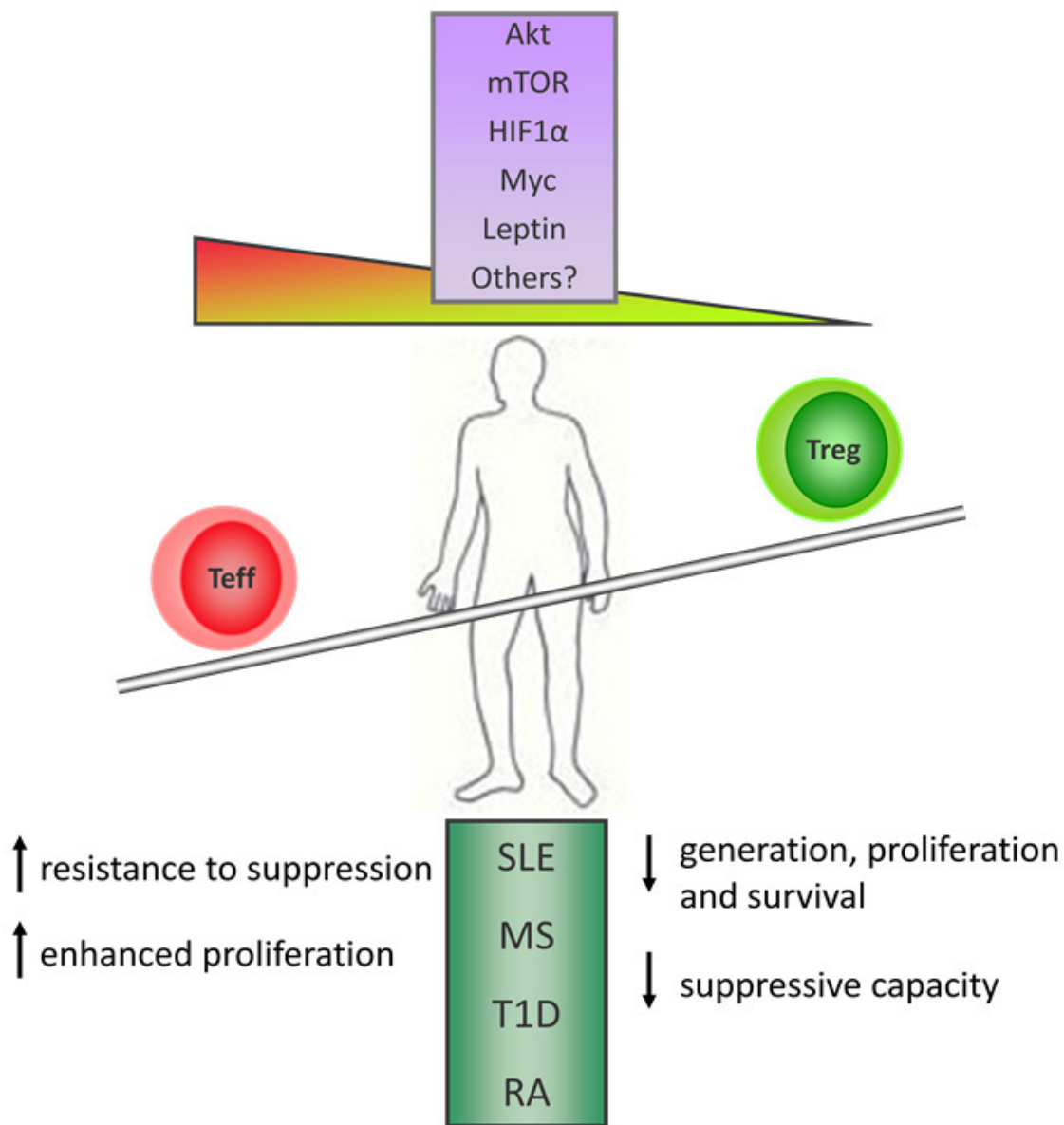


Figure 3. The metabolic factors influencing the immune system and autoimmune diseases. The balance between Treg and Teff function is crucial toward the maintenance of self tolerance. Akt, mTOR, HIF1 α , Myc and Leptin are involved in tipping this balance, and the result of the dampening of Treg function or augmentation of Teff function could lead to the development of SLE, MS, T1D or RA.

Several studies have tried to highlight the genetic and metabolic background that predisposes individuals to autoimmune diseases preceding their onset, but this has been difficult due to the complex network of the different factors involved. A clear risk factor for the development of autoimmunity is represented by the presence of polymorphisms in the Human Leukocyte Antigen (HLA) class II locus, but non-HLA loci have also recently been identified. Some “autoimmune loci”, such as *IL2RA*, *CTLA4*, *IL23R*, *IL10* and *PTPN22* are shared by a wide range of diseases, while others seem to be specific, such as the *VTCN1* (V-set domain containing T cell activation inhibitor 1) locus for SLE [118]. Allelic variants in the *PTPN22* locus, encoding for Lymphoid protein tyrosine phosphatase (Lyp), have been associated with a

high predisposition to autoimmune diseases, including T1D, MS, SLE and RA. Protein tyrosine phosphatases (PTPs) catalyse the release of phosphate groups from tyrosine residues on signalling intermediates, thus playing a fundamental role in activating/deactivating specific transduction pathways. PTPs have been demonstrated to modulate the signalling events following T cell receptor (TCR) engagement with MHC-peptide complexes that lead to the activation and differentiation of T cells [119]. From a metabolic point of view, follow-up studies indicate that specific “lipidomic” profiles, such as low triglycerides, low levels of lysophosphatidylcholine and multiple phospholipids characterize the sera of children that later progress to T1D, as well as anomalies in the levels of glutamine, α -ketoglutarate and other amino acids [120; 121; 122; 123]. The adoption of metabolomics at a high-throughput level has also been useful to uncover these patterns [124]. Vitamin D deficiency has been associated with the increased likelihood of the development of autoimmune disease [125], including type 1 diabetes, and has been linked to key genes involved in the metabolism of 25(OH)D [126]. Despite the lack of direct evidence regarding the behaviour of different T cells subsets prior to the onset of autoimmune diseases, specific alterations in the levels of these modulators can be used to assess an individual's predisposing susceptibility to autoimmunity. Analysing specific T cell markers on a large scale and integrating them with certain genetic and metabolic biomarkers could become a powerful tool for predicting the risk and prognosis of specific autoimmune diseases.

5. Conclusion

Metabolism has an undoubtedly important role in the definition of the T cell repertoire. The constituents of the microenvironment or modulation of T cell responsiveness towards the environment controls the direction in which T cells differentiate. This, in turn, could lead to the development of autoimmune disease if the proinflammatory players prevail against opposing antiinflammatory cues. Although it is becoming clearer as to the role of metabolic networks in defining T cell fate and the development of autoimmunity—the molecular basis, especially the role of miRNAs in controlling T cell metabolism and sensitivity towards extracellular metabolic factors, remain unclear. Various drugs have been produced to tackle tumour growth from a metabolic point of view, and new strategies are emerging to target miRNAs as a therapy. Thus, the lessons learned from these fields may also contribute towards future therapeutic solutions against autoimmunity by specifically targeting T cells at the heart of metabolism.

Author details

Dan Li, Zhimei Gao, Chen Chen, Zuojia Chen,
Jia Nie, Zhao Shan, Yangyang Li, Andy Tsun* and Bin Li*
*Key Laboratory of Molecular Virology & Immunology,
Unit of Molecular Immunology, Institut Pasteur of Shanghai,
Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China*

* Corresponding Author

Miranda Piccioni

*Key Laboratory of Molecular Virology & Immunology,
Unit of Molecular Immunology, Institut Pasteur of Shanghai,
Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China*

*Department of Experimental Medicine and Biochemical Sciences,
Microbiology Section, University of Perugia, Perugia, Italy*

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